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Docket No.: 29915/00281A
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Yan *et al.*,

Application No.: 09/908,943 Group Art Unit: 1652

Filed: July 19, 2001 Examiner: Charles L. Patterson, Jr.

For: SUBSTRATES AND ASSAYS FOR β-SECRETASE ACTIVITY

PETITION FROM IMPROPER RESTRICTION REQUIREMENT PURSUANT TO 37 C.F.R. §1.181 AND §1.144

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Applicants file this petition pursuant to 37 C.F.R. §1.181 and §1.144, to request review and withdrawal of a 442-way restriction requirement imposed by the examiner and made final, notwithstanding a traversal on the merits by the Applicants.

I. Statement of Facts

1. The application as filed included original claims 1-82, which were variously directed to the following related subject matters:

(a) proteins/peptides that are human aspartyl protease substrates (claims 1-35 and 73-82);

(b) polynucleotides that encode the peptide substrates (claims 36-40), and vectors and host cells that comprise the polynucleotides (claims 40-42);

(c) methods of using the substrates to identify modulators of beta secretase/human aspartyl proteases (claims 43-49, 58-67); beta secretase modulators identified by the screening methods (claim 49, 55); and methods of inhibiting beta secretase activity by administering those modulators (claims 50, 56, 57, 68, 69);

(d) methods of producing the substrates (claims 52-54);

(e) kits for performing a beta secretase assay (claims 70-72).

Of the 82 total claims, only 3 are independent (claims 1, 21 and 73); and they are all directed to peptides. A complete list of the claims as filed is attached as Exhibit A. The peptides taught and claimed in the patent application are useful as enzymatic substrates for a human aspartyl protease enzyme implicated in Alzheimer's disease. The substrates may be used in enzymatic activity assays (with the enzyme) to screen for inhibitors of the enzyme, to develop therapeutics designed to inhibit the enzyme.

2. The peptide claims define a genus of peptide substrates using the formula: P_2P_1-$P_1'P_2$, adopting the nomenclature of Schechter and Berger (*Biochem. Biophys. Res. Commun.* 27:157(1967) and *Biochem. Biophys. Res. Commun.* 32:898 (1968), in which the amino acid residues in the peptide substrate that undergo the cleavage are defined as P_1 . . . P_n moving from the scissile bond toward the N-terminus and P_1' . . . P_n' moving from the scissile bond toward the C-terminus. (See specification paragraph bridging pages 18 and 19).

3. The peptides defined by the foregoing formula share common structural features as evident from the genus defined by a single chemical formula wherein each amino acid position near the scissile bond has specified characteristics. Likewise, the peptides share a common functionality due to their common structure, as evinced by the fact that the peptides all serve as peptide substrates that are recognized and cleaved between residue P_1 and P_1' by a particular human aspartyl protease.

4. On September 19, 2002, the Examiner issued the Restriction Requirement (attached as Exhibit B) that is the subject of this petition. The Examiner alleged that pending claims 1-82 were directed to 442 distinct inventions, and required restriction and election. In response, the Applicants filed an election with traverse on November 19, 2002, a copy of which is attached as Exhibit C. Issues identified in the traversal included the following:

(a) the claims of the invention were all related;

(b) the restriction requirement improperly restrict the Applicants to a single species, even thought the rules contemplate examination of "a reasonable number of species" (37 C.F.R. §1.141) and not a single species.

(c) the restriction was incomplete, insofar as certain subject matter within certain claims was not clearly identified as falling within any group;

(d) the restriction was improper insofar as it provided for individual species of the invention to fall within multiple retriction groups.

5. In the first Office action on the merits (Exhibit D), dated February 21, 2003, the Examiner maintained the Restriction Requirement, made it final, and withdrew claims that were directed to non-elected subject matter. (See Exhibit D, page 3.) In maintaining the Restriction Requirement, the Examiner indicated that "it would be a very serious burden on the examiner to examine all of the groups that applicants suggest combining. . . .[because] claims 1 and 21 that are drawn to a multitude of different peptides." (emphasis in original). The Examiner indicated that he could have restricted the Applicants even further but he chose not to. (See page 2 of Exhibit D).

6. Claim 1 as originally filed defines a genus of polypeptides defined by a structural formula. (See Exhibit A.) The genus contains more than 52 individual peptide species.

7. In the restriction requirement, the subject matter of claim 1 was divided into 52 separate groups, each defined by a particular species. (Exhibit B, pp. 2-6, Groups 1-52.)

8. Claim 1 as filed embraces a number of species that do not fall within restriction groups 1-52 and that were not explicitly assigned by the examiner to any other restriction group.

9. An exemplary peptide disclosed in the specification and referenced in at least original claims 20 and 73-78 is SEQ ID NO: 152, which has the following amino acid sequence: SEISY-EVEFR. Applying the Schechter and Berger nomenclature 2), SEQ ID NO:152 is written as $P_5P_4P_3P_2P_1$--$P_1'P_2'P_3'P_4'P_5'$, wherein P_5 is S; P_4 is E; P_3 is I; P_2 is S; P_1 is Y; $P_{1'}$ is E; $P_{2'}$ is V; $P_{3'}$ is E, $P_{4'}$ is F, and $P_{5'}$ is R.

10. A peptide satisfying SEQ ID NO: 152 falls into at least six different restriction groups as defined by the examiner:

(a) Group 31 defines an allegedly independent and distinct group with the sequence SEQ ID NO: 152;

(b) Group 54 defines an allegedly independent and distinct group with the requirement that P_2 be S. In SEQ ID NO: 152, P_2 is S. Thus, a peptide comprising SEQ ID NO: 152 falls within Group 54.

(c) Group 56 defines an allegedly independent and distinct group with the requirement that P_1 be Y. In SEQ ID NO: 152, P_1 is Y. Thus, a peptide comprising SEQ ID NO: 152 falls within Group 56.

(d) Group 59 defines an allegedly independent and distinct group with the requirement that $P_{1'}$ be E. In SEQ ID NO: 152, $P_{1'}$ is E. Thus, a peptide comprising SEQ ID NO: 152 falls within Group 59.

(e) Group 63 defines an allegedly independent and distinct group with the requirement that $P_{2'}$ be V. In SEQ ID NO: 152, $P_{2'}$ is V. Thus, a peptide comprising SEQ ID NO: 152 falls within Group 63.

(f) Group 442 includes claim 73, which explicitly recites SEQ ID NO: 152.

11. Numerous other peptides of the invention besides SEQ ID NO: 152 , fall within two or more restriction groups because the groups do not define independent or distinct inventions.

12. By obvious extension, the analysis in paragraph 8 is equally applicable to restriction groups 64-126, which define polynucleotide subject matter; restriction groups

127-378, which define various method subject matter; and groups 379-441, directed to kits. In each instance, the Examiner used the alleged independence or distinctness of the peptide groups 1-63 as a basis for restricting the other categories of subject matter. In fact, groups 127-441 were not individually defined, except to specify that they corresponded to be peptide groups 1-63.

13. As exemplified in claim 21 as filed, P_1 may be selected from the group consisting of Y, L, and Nle; $P_{1'}$ may be selected from the group consisting of E, A and D.

14. Based on filing as a large entity, as of October 1, 2003, the basic filing fee for utility application is $770.00, a utility issue fee is $1330.00, and the first, second and third maintenance fees are $910.00, $2090.00, and $3220.00, respectively.

II. Legal Authority upon Which Instant Petition is based

37 C.F.R. §1.181 provides that petition may be taken to the Commissioner in "cases in which a statute or the rules specify that the matter is to be determined directly by or reviewed by the Commissioner." (37 C.F.R. §1.181.) According to 37 C.F.R. §1.144, "[a]fter a final requirement for restriction, the applicant, in addition to making any reply due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal."

According to the Patent Office guidelines set forth in the MPEP, restriction practice under 35 U.S.C. §121 allows the Commissioner discretion to require restriction between two or more "independent and distinct" inventions (See M.P.E.P. 802.01 defining independent and distinct). M.P.E.P. 802.01 defines "independent" in relation to this practice, to mean:

> "that there is no disclosed relationship between the two or more subjects disclosed, that is, they are ***unconnected in design, operation, or effect***, for example: (1) species under a genus which species are not usable together as disclosed; or (2) process and apparatus incapable of being used in practicing the process."

As stated in MPEP §806.04(a), the rules provide that a reasonable number of species may still be claimed in one application. Moreover, the MPEP requires that "where there is a relationship disclosed between the species, such disclosed relation must be discussed and reasons advanced leading to the conclusion that the disclosed relation does not prevent restriction, in order to establish the propriety of restriction." MPEP §808.01(a). Even when restriction is proper, the MPEP requires that the Examiner should clearly identify each of the disclosed species to which claims are restricted and identify the distinguishing characteristics of species. See, e.g., MPEP §809.02(a).

III. Requested Relief and Reasons Relief Should be Granted

This petition is filed pursuant to 37 C.F.R. §1.181 and §1.144 to request review of the final restriction for requirement in this case. Applicants timely traversed the restriction requirement. (See Fact paragraph 4). Upon reconsideration, the Examiner made the restriction requirement final (Fact 5).

The present case was filed with three independent and 82 total claims, all related in that they defined a protein/peptide substrate of an aspartyl protease referred to as Asp2, or defined materials or methods of making and using the same. (Facts 1-3.)

It is both axiomatic and required by the patent statute that claims only be restricted when they define independent and distinct inventions. The current restriction requirement is defective insofar as it specifies 442 overlapping groups such that individual species of the invention fall within multiple groups. (Facts 9-12.) It is impossible for restriction groups to be "independent" or "distinct" from one another when the same polypeptide falls within at least six of the groups.

The restriction requirement is further facially defective because it fails to clearly assign the entirety of the claimed subject matter to individual groups. For example, original claim 1 was split into fifty-two distinct groups which each define a particular peptide species, yet the claim 1 actually encompasses more than 52 species. (Facts 6-8).

The Examiner arrived at 442-ways Restriction Requirement by splitting each of the claims into multiple groups in such a manner as to ignore the unifying, "linking" characteristic for the claims, namely, that they are all directed to structurally related peptide

substrates recognized by a single enzyme and materials and methods for making and using the peptide substrates. The substrates can be defined by simple chemical formula. (Facts 2-3).

The claims of the present invention are not "independent" as defined in MPEP 802.01, which interprets "independent" to mean that the two or more disclosed embodiments "are ***unconnected in design, operation, or effect***, for example: (1) species under a genus which species are not usable together as disclosed; or (2) process and apparatus incapable of being used in practicing the process." Taking for example the peptide/polypeptide subject matter of claims 1-35 and 73-82, the subject matter of those claims is ***directly connected*** in design (*i.e.*, the protein or peptide sequences all comprise a scissile bond that is cleaved by a human aspartyl protease). The various peptide/polypeptide substrates are all species of the same genus that has been defined by using the simple formula P_2P_1--$P_1'P_2'$. Each of these peptides operates in the same manner (*i.e.*, the peptides are cleaved by human aspartyl protease), and have the same effect (*i.e.*, mimic the effects of wild-type substrate for human aspartyl protease). Therefore, the claims to the individual peptides cannot properly be classified as independent of each other.

Moreover, the M.P.E.P. instructs Examiners that "if a search and examination of an entire application can be made without serious burden, the examiner ***must examine it on its merits even if it includes claims to independent or distinct inventions***."

Under the current restriction requirement, if the Applicant wished to prosecute all 442 groups to issuance, the Applicant would be forced to pay over $340,000 in basic filing fees; over $587,000 in issue fees; and approximately $2.75 million in maintenance fees. (Assuming no increases from the fee schedule effective October 1, 2003, over the life of the eventual patents.) In addition, the Applicant would be forced to pay substantial attorney fees for prosecution, and the public would be burdened by the need to evaluate several hundred related patents for infringement purposes. The absurdity of this situation may be alleviated by reformulating the restriction requirement to conform to more traditional restriction practice. One such alternative was suggested by the Applicants in response to the original restriction requirement.

In the event that the Commissioner agrees with the Examiner that it would be too burdensome to examine all of the peptides encompassed by the formulae of depicted in the claims, an alternative restriction to the suggestion set forth in Applicants' original traversal of the restriction requirement that would greatly reduce the number of peptides being examined would be one in which the peptides of the invention are restricted according to the amino acids that are located at positions P_1 and $P_{1'}$ (See fact paragraph 15). In restricting the claims in such a fashion, a new restriction requirement may be articulated in which 9 Groups are suggested as follows:

Group I: An isolated peptide defined by the formula P_2P_1-$P_{1'}P_{2'}$, wherein P_1-$P_{1'}$ is Y-E; kits comprising the same; polynucleotides encoding the same and methods of making or using the same

Group II: An isolated peptide defined by the formula P_2P_1-$P_{1'}P_{2'}$, wherein P_1-$P_{1'}$ is Y-A; kits comprising the same; polynucleotides encoding the same and methods of making or using the same;

Group III: An isolated peptide defined by the formula P_2P_1-$P_{1'}P_{2'}$, wherein P_1-$P_{1'}$ is Y-D; kits comprising the same; polynucleotides encoding the same and methods of making or using the same;

Group IV: An isolated peptide defined by the formula P_2P_1-$P_{1'}P_{2'}$, wherein P_1-$P_{1'}$ is L-E; kits comprising the same; polynucleotides encoding the same and methods of making or using the same;

Group V: An isolated peptide defined by the formula P_2P_1-$P_{1'}P_{2'}$, wherein P_1-$P_{1'}$ is L-A; kits comprising the same; polynucleotides encoding the same and methods of making or using the same;

Group VI: An isolated peptide defined by the formula P_2P_1-$P_{1'}P_{2'}$, wherein P_1-$P_{1'}$ is L-D; kits comprising the same; polynucleotides encoding the same and methods of making or using the same;

Group VII: An isolated peptide defined by the formula P_2P_1-$P_{1'}P_{2'}$, wherein P_1-$P_{1'}$ is Nle-E; kits comprising the same; polynucleotides encoding the same and methods of making or using the same;

Group VIII: An isolated peptide defined by the formula P_2P_1-$P_1'P_2'$, wherein P_1-P_1' is Nle-A; kits comprising the same; polynucleotides encoding the same and methods of making or using the same;

Group IX: An isolated peptide defined by the formula P_2P_1-$P_1'P_2'$, wherein P_1-P_1' is Nle-D; kits comprising the same; polynucleotides encoding the same and methods of making or using the same;

Applicants submit that peptides of the invention should be examined together with the methods of using those peptides in the intended screening methods for which the peptides have been designed, as any search designed to identify substrates of human aspartyl protease also will identify methods of using those substrates in assays that determine human aspartyl protease activity.

As compared to the Examiner's 442-way restriction, reformulation into the above nine groups has several advantages. First, these groups (unlike the groups restricted by the examiner) define non-overlapping genera. Second these groups strike a fair balance between reducing the burden on the examiner and permitting the applicants to claim substantial aspects of their invention in a reasonable number of divisional applications.

IV. Conclusions

Applicants believe that the Restriction Requirement in the instant case requires review by the Commissioner, and therefore Applicants request that this petition be granted. No fee is believed to be due with the filing of a petition pursuant to 37 C.F.R. §1.144 and 37 C.F.R. §1.181, however, should a fee be deemed necessary in connection with the filing of this petition the Commissioner is hereby authorized to deduct such a fee from Marshall, Gerstein and Borun account number 13-2855.

Dated: March 15, 2004

Respectfully submitted,

By _____

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WHAT IS CLAIMED IS:

1. An isolated peptide comprising a sequence of at least four amino acids defined by formula P_2P_1--$P_1'P_2'$ wherein

P_2 is a charged amino acid, a polar amino acid, or an aliphatic amino acid but is not an aromatic amino acid;

P_1 is an aromatic amino acid or an aliphatic amino acid but not a polar amino acid or a charged amino acid;

P_1' is a charged amino acid, or aliphatic amino acid, or a polar amino acid but is not an aromatic amino acid;

P_2' is an uncharged aliphatic polar amino acid or an aromatic amino acid; and

wherein said peptide is cleaved between P_1 and P_1' by a human aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:3 and said peptide does not comprise the corresponding P_2P_1--$P_1'P_2'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

2. The isolated peptide of claim 1, comprising an amino acid sequence defined by formula P_2P_1--$P_1'P_2'P_3'$, wherein P_3' is any amino acid, and wherein said peptide does not comprise the corresponding P_2P_1--$P_1'P_2'P_3'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

3. The isolated peptide of claim 1, comprising an amino acid sequence defined by formula $P_3P_2P_1$--$P_1'P_2'P_3'$, wherein P_3 is an uncharged polar amino acid, an uncharged aliphatic amino acid, or an aromatic amino acid, and wherein said said peptide does not comprise the corresponding $P_3P_2P_1$--$P_1'P_2'P_3'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

4. The isolated peptide of claim 3, comprising an amino acid sequence defined by formula $P_4P_3P_2P_1$--$P_1'P_2'P_3'$, wherein said P_4 is a charged amino acid, a polar amino acid or an aliphatic amino acid but not an aromatic amino acid and said peptide does not comprise the corresponding $P_4P_3P_2P_1$--$P_1'P_2'P_3'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

5. The isolated peptide of any one of claims 2 through 4, further comprising an amino acid at position P_4' immediately to the carboxy-terminal position of P_3' wherein said P_4' is any amino acid said, and wherein the peptide does not comprise the corresponding $P_3P_2P_1$--$P_1'P_2'P_3'$ P_4' portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

6. The isolated peptide of claim 1, wherein said P_2 is an amino acid selected from the group consisting of N, L, K, S, G, T, D, A, Q and E.

7. The isolated peptide of claim 1, wherein said P_1 is an amino acid selected from the group consisting of Y, L, M, Nle, F, and H.

8. The isolated peptide of claim 1, wherein said P_1' is an amino acid selected from the group consisting of E, A, D, M, Q, S and G.

9. The isolated peptide of claim 1, wherein said P_2' is an amino acid selected from the group consisting of V, A, N, T, L, F, and S.

10. The isolated peptide of claim 2, wherein said P_3' is an amino acid selected from the group consisting of E, G, F, H, cysteic acid and S.

11. The isolated peptide of claim 3, wherein said P_3 is an amino acid selected from the group consisting of A, V, I, S, H, Y, T and F.

12. The isolated peptide of claim 4, wherein said P_4 is an amino acid selected from the group consisting of E, G, I, D, T, cysteic acid and S.

13. The isolated peptide of any one of claims 4-12, wherein said P_4' is an amino acid selected from the group consisting of F, W, G, A, H, P, G, N, S, and E.

14. The isolated peptide of any one of claims 1 through13 further comprising a first label.

15. The isolated peptide of claim 14 further comprising a second label.

16. An isolated peptide according to any one of claims 1-13, further comprising a detectable label and a quenching moiety, wherein cleavage of the peptide between P_1 and P_1' separate the quenching moiety from the label to permit detection of the label.

17. The isolated peptide of claim 10 or 12, wherein said cysteic acid further comprises a covalently attached label.

18. The isolated peptide of any one of claims 1-17, wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP β-secretase cleavage sequence: SEVKM-DAEFR (SEQ ID NO:20).

19. The isolated peptide of any one of claims 1-17, wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP Swedish KM→NL mutation, β-secretase cleavage sequence SEVNL-DAEFR (SEQ ID NO:19).

20. The isolated peptide of claim 1, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17, SEQ ID NO:18; SEQ ID NO:120; SEQ ID NO:133; SEQ ID NO:134; SEQ ID NO:135; SEQ ID NO:136; SEQ ID NO:137; SEQ ID NO:138; SEQ ID NO:141; SEQ ID NO:143; SEQ ID NO:144; SEQ ID NO:145; SEQ ID NO:147; SEQ ID NO:148; SEQ ID NO:149; SEQ ID NO:150; SEQ ID NO:151; SEQ ID NO:152; SEQ ID NO:153; SEQ ID NO:154; SEQ ID NO:155; SEQ ID NO:156; SEQ ID NO:157; SEQ ID NO:158; SEQ ID NO:159; SEQ ID NO:160; SEQ ID NO:161; SEQ ID NO:162; SEQ ID NO:163; SEQ ID NO:164; SEQ ID NO:165; SEQ ID NO:166; SEQ ID NO:167; SEQ ID NO:168; SEQ ID NO:169; SEQ ID NO:190; SEQ ID NO:191; SEQ ID NO:192 and SEQ ID NO:193.

21. An isolated peptide comprising a sequence of at least four amino acids

defined by formula P_2P_1--$P_1'P_2'$, wherein:

P_2 comprises an amino acid selected from the group consisting of N, S, and D;

P_1 comprises an amino acid selected from the group consisting of Y, L, and Nle;

P_1' comprises an amino acid selected from the group consisting of E, A, and D;

P_2' comprises an amino acid selected from the group consisting of A and V; and

wherein a human Aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3 (Hu-Asp2) cleaves said peptide between P_1 and P_1';

with the proviso that if $P_1'P_2'$ comprise the sequence DA, P_2P_1 do not comprise the sequences NL or NNle.

22. An isolated peptide according to claim 21, wherein the peptide amino acid sequence consists of 4-50 amino acids.

23. An isolated peptide according to claim 21, wherein the Hu-Asp2 cleaves the peptide at a rate greater than the Hu-Asp2 cleaves a corresponding peptide having the P_2P_1--$P_1'P_2'$ amino acid sequence KMDA.

24. An isolated peptide according to claim 21, wherein the Hu-Asp2 cleaves the peptide at a rate greater than the Hu-Asp2 cleaves a corresponding peptide having the P_2P_1--$P_1'P_2'$ amino acid sequence KMDA.

25. A peptide according to claim 21, further comprising a label.

26. A peptide according to claim 21, further comprising a label and a quenching moiety that quenches the label, wherein the label and quenching moiety are

attached on opposite sides of the P_1--P_1 peptide bind, whereby cleavage of the P_1--P_1 peptide bond separates the label and quenching moiety.

27. A polypeptide comprising a peptide sequence according to claim 21, and further comprising a transmembrane domain to localize the polypeptide to a cellular membrane when the polypeptide is expressed in a eukaryotic cell.

28. A polypeptide comprising a peptide according to any one of claims 1 through 20 and further comprising a transmembrane domain amino acid sequence.

29. A polypeptide according to claim 28, wherein the peptide is N-terminal to the transmembrane domain.

30. The polypeptide of claim 28 or 29, wherein the peptide and the transmembrane domain are separated by a linker.

31. The polypeptide of claim 30, wherein said linker is a peptide linker comprising between about 20 to about 40 amino acids.

32. The polypeptide according to any one of claims 28-31, wherein said transmembrane domain anchors said polypeptide to an intracellular membrane selected from the group consisting of the Golgi or the endoplasmic reticulum.

33. The fusion protein of any of claims 28-32, wherein said transmembrane domain is selected from the group consisting of the transmembrane domain of galactosyltransferase, the transmembrane domain of sialyly transferase; the transmembrane domain of human aspartyl transferase 1; the transmembrane domain of human aspartyl transferase 2; the transmembrane

domain of syntaxin 6; the transmembrane domain of ubiquitin; the transmembrane domain of insulin B chain and the transmembrane domain of APP.

34. The polypeptide according to any one of claims 28-32, further comprising a reporter protein amino acid sequence.

35. The polypeptide of claim 34, wherein said reporter protein is selected from the group consisting of luciferase; alkaline phosphatase; β-galactosidase; β-glucorinidase; green fluorescent protein; chloramphenical acetyl transferase;

36. A polynucleotide comprising a nucleotide sequence that encodes a polypeptide according to any one of claims 20-35.

37. A polynucleotide comprising a nucleotide sequence that encodes a peptide according to any one of claims 1-27.

38. A vector comprising a polynucleotide according to claim 36.

39. A vector comprising a polynucleotide according to claim 37.

40. A vector according to claim 38 wherein said polynucleotide is operably linked to a promoter to promote expression of the fusion protein encoded by the polynucleotide in a host cell.

41. A host cell transformed or transfected with a polynucleotide according to claim 36.

42. A host cell transformed or transfected with a vector according to any one of claims 38-40.

43. A method for assaying for modulators of β-secretase activity, comprising the steps of:

(a) contacting a first composition with a second composition both in the presence and in the absence of a putative modulator compound, wherein the first composition comprises a mammalian β-secretase polypeptide or biologically active fragment thereof, and wherein the second composition comprises a substrate, wherein said substrate comprises a peptide according to any of claims 1 through 26 or a polypeptide according to any of claims 27-35;

(b) measuring cleavage of the substrate peptide in the presence and in the absence of the putative modulator compound; and

(c) identifying modulators of β-secretase activity from a difference in cleavage in the presence versus in the absence of the putative modulator compound, wherein a modulator that is a β-secretase antagonist reduces such cleavage and a modulator that is a β-secretase agonist increases such cleavage.

44. The method of claim 43, wherein said first composition comprises a purified human Asp2 polypeptide.

45. The method of claim 43, wherein said first composition comprises a soluble fragment of a human Asp2 polypeptide that retains Asp2 β-secretase activity.

46. The method of claim 45, wherein said soluble fragment is a fragment lacking an Asp2 transmembrane domain.

47. A method according to claim 43, wherein the β-secretase polypeptide of the first composition comprises a polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the β-secretase polypeptide.

48 A method according to claim 43, wherein the polypeptide of the first composition is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide, and wherein the measuring step comprises measuring APP processing activity of the cell.

49. The method claim of any of claims 43-48, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2.

50. A β-secretase modulator identified according to the method of any of claims 43-48.

51. A method of inhibiting β-secretase activity *in vivo* comprising a step of administering a modulator according to claim 50 that is a β-secretase antagonist to a mammal in an amount effective to inhibit β-secretase in cells of said mammal.

52. A method of producing a substrate for a β-secretase assay comprising:

growing a host cell transformed or transfected with a vector of claim 40 in a manner allowing expression of said polypeptide.

53. The method of claim 52, further comprising purifying said polypeptide.

54. The method of claim 52, wherein said host cell is selected from the group consisting of a mammalian host cell, a bacterial host cell and a yeast host cell.

55. A pharmaceutical composition comprising a modulator of claim 50 and a pharmaceutically acceptable carrier.

56. A method of treating a disease or condition characterized by an abnormal β-secretase activity comprising administering to a subject in need of treatment a pharmaceutical composition of claim 55.

57. A use of a modulator identified according to the method claim 43 in the manufacture of a medicament for the treatment of Alzheimer's Disease.

58. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) contacting a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27-35 and a composition comprising an Hu-Asp2 activity in the presence and absence of a test agent;

(b) determining the cleavage of said peptide or polypeptide between said P_1 and P_1' by said Hu-Asp2 in the presence and absence of the test agent; and

(c) comparing said cleavage activity of the Hu-Asp2 in the presence of the test agent to the activity in the absence of the test agent to identify an agent that inhibits said cleavage by the Hu-Asp2, wherein reduced activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

59. A method according to claim 58, wherein the Hu-Asp2 is a recombinant Hu-Asp2 purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes Hu-Asp2.

60. A method according to claim 58,

wherein the Hu-Asp2 is expressed in a cell, wherein the contacting comprises growing the cell in the presence and absence of the test agent, and

wherein the determining step comprises measuring cleavage of said peptide or fusion protein.

61. A method according to claim 60, wherein the cell further comprises a polynucleotide encoding the polypeptide, and wherein the contacting step comprises growing the cell under conditions in which the cell expresses the polypeptide.

62. A method according to claim 60 or 61, wherein the cell is a human embryonic kidney cell line 293 cell.

63. A method according to any one of claims 59-62 wherein the nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 2;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 4;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 2) or Hu-Asp2(b) (SEQ ID NO: 4), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.

64. A method for identifying agents that modulate the activity of Asp2 aspartyl protease, comprising the steps of:

(a) contacting an Asp2 aspartyl protease and a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35 in the

presence and absence of a test agent, wherein the Asp2 aspartyl protease is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3;

(b) determining the cleavage of said peptide or fusion protein between said P_1 and said P_1' site by said Asp2 in the presence and absence of the test agent; and

(c) comparing the cleavage activity of said Asp2 in the presence of the test agent to the cleavage activity in the absence of the agent to identify agents that modulate the activity of the polypeptide, wherein a modulator that is an Asp2 inhibitor reduces said cleavage and a modulator that is an Asp2 agonist increases said cleavage.

65. A method according to 58 or 64, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2.

67. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) growing a cell in the presence and absence of a test agent, wherein the cell expresses an Hu-Asp2 and expresses a protein comprising a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35;

(b) determining the determining the cleavage of said protein at the site between said P_1 and P_1' in said cell in the presence and absence of the test agent; and

(c) comparing said cleavage activity in the presence of the test agent to the cleavage activity in the absence of the test agent to identify an agent that inhibits the activity of Hu-Asp2, wherein reduced cleavage activity in the presence of the test

agent identifies an agent that inhibits Hu-Asp2 activity.

67. A method according to claim 67, wherein the host cell has been transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes a Hu-Asp2, wherein said nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 2;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 4;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 2) or Hu-Asp2(b) (SEQ ID NO: 4), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.

68. A method according to any one of claims 66-67, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

69. The use of an agent identified as an inhibitor of Hu-Asp2 according to any one of claims 66-67 in the manufacture of a medicament for the treatment of Alzheimer's Disease.

70. A kit for performing a β-secretase assay comprising a β-secretase substrate comprising a peptide according to any of claims 1 through 27 and a β-secretase enzyme.

71. The kit of claim 70, wherein said β-secretase substrate is a polypeptide according to any of claims 28-35.

72. The kit of claim 70 or 71, further comprising reagents for detecting the cleavage of said peptide or fusion protein.

73. An isolated peptide comprising a sequence of at least 10 amino acids having the sequence SEISY-EVEFR (SEQ ID NO:152).

74. The isolated peptide of claim 73, wherein said peptide comprises at least 3 amino acids immediately to the carboxy-terminal of SEISY-EVEFR (SEQ ID NO:152).

75. The isolated peptide of claim 73, wherein said peptide comprises at least 3 amino acids immediately to the amino-terminal of SEISY-EVEFR (SEQ ID NO:152).

76. The isolated peptide of claim 73, wherein said peptide comprises at least 5 amino immediately to the carboxy-terminal of SEISY-EVEFR (SEQ ID NO:152).

77. The isolated peptide of claim 73, wherein said peptide comprises at least 5 amino immediately to the amino-terminal of SEISY-EVEFR (SEQ ID NO:152).

78. The isolated peptide of claim 73, wherein said peptide comprises at least 10 amino immediately to the amino-terminal of SEISY-EVEFR (SEQ ID NO:152).

79. The isolated peptide of claim 73, wherein said peptide comprises at least 13 amino acids.

80. The isolated peptide of claim 73, wherein said peptide comprises at least 15 amino acids.

81. The isolated peptide of claim 73, wherein said peptide comprises at least 20 amino acids.

82. The isolated peptide of claim 73, wherein said peptide comprises at least 50 amino acids.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/908,943	07/19/2001	Riqiang Yan	29915/00281A.US	1034

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EXAMINER	
PATTERSON, CHARLES L JR	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/19/2002

Docketed: 10/19/02

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/908,943	YAN ET AL.	
	Examiner	Art Unit	
	Charles L. Patterson, Jr.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-82 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-82 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

There are handwritten interlineations changing claim 58 to 64 and 67 and 68 to 66 and 67. These interlineations are not initialed and therefore they need to be corrected by amendment. The claim number they have been changed to are referred to in the instant restriction requirement as they would have been changed under 37 CFR 1.126 if no interlineations had been made.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

1. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 5, classified in class 530, subclass 327.
2. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 6, classified in class 530, subclass 326.
3. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 7, classified in class 530, subclass 327.
4. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 8, classified in class 530, subclass 328.
5. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 9, classified in class 530, subclass 328.
6. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 10, classified in class 530, subclass 328.
7. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 11, classified in class 530, subclass 328.
8. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 12, classified in class 530, subclass 328.
9. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 13, classified in class 530, subclass 328.

10. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 14, classified in class 530, subclass 328.

11. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 15, classified in class 530, subclass 328.

12. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 16, classified in class 530, subclass 328.

13. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 17, classified in class 530, subclass 328.

14. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 18, classified in class 530, subclass 328.

15. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 120, classified in class 530, subclass 328.

16. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 133, classified in class 530, subclass 328.

17. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 134, classified in class 530, subclass 328.

18. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 135, classified in class 530, subclass 328.

19. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 136, classified in class 530, subclass 328.

20. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 137, classified in class 530, subclass 328.

21. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 138, classified in class 530, subclass 328.

22. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 141, classified in class 530, subclass 328.

23. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 143, classified in class 530, subclass 328.

24. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 144, classified in class 530, subclass 328.

25. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 145, classified in class 530, subclass 324.

26. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 147, classified in class 530, subclass 326.

27. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 148, classified in class 530, subclass 328.

28. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 149, classified in class 530, subclass 328.

29. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 150, classified in class 530, subclass 328.

30. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 151, classified in class 530, subclass 328.

31. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 152, classified in class 530, subclass 328.

32. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 153, classified in class 530, subclass 328.

33. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 154, classified in class 530, subclass 327.

34. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 155, classified in class 530, subclass 326.

35. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 156, classified in class 530, subclass 325.

36. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 157, classified in class 530, subclass 324.

37. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 158, classified in class 530, subclass 327.

38. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 159, classified in class 530, subclass 326.

39. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 160, classified in class 530, subclass 326.

40. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 161, classified in class 530, subclass 324.

41. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 162, classified in class 530, subclass 327.

42. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 163, classified in class 530, subclass 326.

43. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 164, classified in class 530, subclass 326.

44. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 165, classified in class 530, subclass 324.

45. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 166, classified in class 530, subclass 327.

46. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 167, classified in class 530, subclass 326.

47. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 168, classified in class 530, subclass 326.

48. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 169, classified in class 530, subclass 324.

49. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 190, classified in class 530, subclass 327.

50. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 191, classified in class 530, subclass 326.

51. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 192, classified in class 530, subclass 326.

52. Claims 1-20, 28-35, drawn to a peptide of SEQ ID NO: 193, classified in class 530, subclass 326.

53. Claims 21-27, drawn to a peptide wherein P_2 is N, classified in class 530, subclass 330.

54. Claims 21-27, drawn to a peptide wherein P_2 is S, classified in class 530, subclass 330.

55. Claims 21-27, drawn to a peptide wherein P_2 is D, classified in class 530, subclass 330.

56. Claims 21-27, drawn to a peptide wherein P_1 is Y, classified in class 530, subclass 330.

57. Claims 21-27, drawn to a peptide wherein P_1 is L, classified in class 530, subclass 330.

58. Claims 21-27, drawn to a peptide wherein P_1 is Nle, classified in class 530, subclass 330.

59. Claims 21-27, drawn to a peptide wherein P_1' is E, classified in class 530, subclass 330.

60. Claims 21-27, drawn to a peptide wherein P_1' is A, classified in class 530, subclass 330.

61. Claims 21-27, drawn to a peptide wherein P_1' is D, classified in class 530, subclass 330.

62. Claims 21-27, drawn to a peptide wherein P_2' is A, classified in class 530, subclass 330.

63. Claims 21-27, drawn to a peptide wherein P_2' is V, classified in class 530, subclass 330.

64-126. Claims 36-42 and 52-54, drawn to a polynucleotide that encodes the polypeptide of claims 1-35, a vector, a host cell and method of producing a substrate for a β-secretase assay, classified in class 435, subclass 320.1 and 252.3 and class 536, subclass 232.1. The groups 64-126 correspond to groups 1-63.

127-189. Claims 43-50, drawn to a method for assaying for modulators of β-secretase activity, a method of inhibiting β-secretase activity *in vivo*, classified in class 435, subclass 23. The groups 127-189 correspond to groups 1-63.

190-252. Claims 51 and 55-57, drawn to a method of inhibiting the β-secretase activity *in vivo* comprising administering a modulator according to claim 50, a pharmaceutical composition comprising a modulator, a method of treating a disease comprising administering the pharmaceutical composition and the use of a modulator to treat Alzheimer's Disease, classified in various classes and subclasses depending upon what the inhibitor is. The groups 190-252 correspond to groups 1-63.

253-315. Claims 58-64, 66-67, drawn to a method for identifying agents the inhibit Asp2 aspartyl protease and a method of identifying agents that modulate Asp2 aspartyl protease, classified in class 435, subclass 219. The groups 252-315 correspond to groups 1-63.

316-378. Claims 65 and 68-69, drawn to a method of treating Alzheimer's Disease comprising using an inhibitor of Hu-Asp2, classified in various classes and subclasses depending upon the identity of the inhibitor. The groups 316-378 correspond to groups 1-63.

379-441. Claim 70-72, drawn to a kit for performing a β-secretase assay, classified in class 435, subclass 23. The groups 379-441 correspond to groups 1-63.

442. Claims 73-82, drawn to a peptide, classified in class 530, subclass 328, 327, 326 and 324.

The inventions are distinct, each from the other because:

Groups (1-63) and (64-126) are drawn to completely different chemical compounds that are patentably distinct. Groups (1-63) and 442 are drawn to different structural peptides and as such are patentable distinct from each other. The other groupings correspond to groups 1-63 because they all depend upon groups 1-63.

Inventions (1-63) and (127-189) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process such as in the methods of groups (190-252), (253-315), (316-378) and in the kit or groups (379-441).

Inventions (1-63) and (190-252) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can

be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process such as in the methods of groups (127-189), (253-315), (316-378) and in the kit or groups (379-441).

Inventions (1-63) and (253-315) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process such as in the methods of groups (127-189),(190-252), (316-378) and in the kit or groups (379-441).

Inventions (1-63) and (316-378) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process such as in the methods of groups (127-189), (190-252), (253-315), and in the kit or groups (379-441).

Inventions (379-441) are drawn to a product (a kit) that is patentably distinct from the products of groups (1-63) and (64-126).

Claim 33 is presumed to be drawn to a polypeptide instead of a fusion protein, since there is no antecedent basis for fusion protein in claims 28-32.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 703-308-1834. The examiner can normally be reached on Monday - Friday, 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
September 19, 2002

PATENT

P&U Ref. No. 00281.US1

Attorney Docket No: 29915/00281A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Yan et al.

Serial No.: 09/908,943

Filed: July 19, 2001

For: SUBSTRATES AND ASSAYS FOR BETA SECRETASE

Group Art Unit: 1652

Examiner: Charles L. Patterson

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231 on this date:

November 19, 2002

Nabeela R. McMillian
Reg. No. 43,363
Agent for Applicants

ELECTION WITH TRAVERSE IN RESPONSE TO RESTRICTION REQUIREMENT

Commissioner for Patents
Washington, DC 20231

Sir:

In a restriction requirement dated September 19, 2002, in the above-identified matter, the Patent Office alleged that pending claims 1-82 were directed to 442 distinct inventions, and required restriction. Applicants' response is timely filed by virtue of the attached petition and fee for a one month extension of time to respond, extending the deadline for the response to November 19, 2002. Reconsideration is requested in view of the following remarks. No fees are believed to be due in connection with this response, however, should there be any fees be necessary, the Commissioner is hereby authorized to charge any such fees to deposit account No. 13-2855.

AMENDMENTS

IN THE CLAIMS

Please amend the claims as follows to effect renumbering of the second claim 58, originally filed claim 67 and first claim 68 as follows:

64. A method for identifying agents that modulate the activity of Asp2 aspartyl protease, comprising the steps of:

(a) contacting an Asp2 aspartyl protease and a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35 in the presence and absence of a test agent, wherein the Asp2 aspartyl protease is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3;

(b) determining the cleavage of said peptide or fusion protein between said P_1 and said P_1' site by said Asp2 in the presence and absence of the test agent; and

(c) comparing the cleavage activity of said Asp2 in the presence of the test agent to the cleavage activity in the absence of the agent to identify agents that modulate the activity of the polypeptide, wherein a modulator that is an Asp2 inhibitor reduces said cleavage and a modulator that is an Asp2 agonist increases said cleavage.

66. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) growing a cell in the presence and absence of a test agent, wherein the cell expresses an Hu-Asp2 and expresses a protein comprising a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35;

(b) determining the determining the cleavage of said protein at the site between said P_1 and P_1' in said cell in the presence and absence of the test agent; and

(c) comparing said cleavage activity in the presence of the test agent to the cleavage activity in the absence of the test agent to identify an agent that inhibits the activity of Hu-Asp2, wherein reduced cleavage activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

67. A method according to claim 66, wherein the host cell has been transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes a Hu-Asp2, wherein said nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 2;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 4;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 2) or Hu-Asp2(b) (SEQ ID NO: 4), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.

REMARKS

I. Explanation of Amendments to the Specification and Claims

The Examiner noted that there were interlineations changing claim 58 to 64 and 67 and 68 to 66 and 67. Applicants apologize that the claims as originally filed were inadvertently misnumbered. Applicants have renumbered the claims to ensure there is consecutive numbering of all of the claims. Applicants also amended claim 67 to refer to claim 66 to ensure proper antecedent basis. A complete set of the claims with the correct numbering is attached herewith as Appendix A.

II. Restriction and Election

Citing 35 U.S.C. § 121, the Examiner alleged that claims 1-82 were drawn to 442 distinct inventions.

The Applicants hereby elect Group 56, which includes Claims 21-27, drawn to a peptide of a generic sequence in which P_1 is Y. Applicants make these elections ***with traverse.***

III. Applicants Traversal of the Restriction Requirement.

The application contains 82 claims which are all related in that they involve (I) proteins/peptide that are human aspartyl protease substrates (claims 1-35 and 73-82), (II) polynucleotides and vectors for encoding those substrates (claims 36-40), (III) host cells transformed or transfected with polynucleotides or vectors encoding the substrates (claims 40-42), (IV) methods of using the substrates to identify modulators of beta secretase/human aspartyl proteases (claims 43-49, 58-67), (V) beta secretase modulators identified by the screening methods (claim 49, 55), (VI) methods of inhibiting beta secretase activity by administering those modulators (claims 50, 56, 57, 68, 69), (VII) methods of producing the substrates (claims 52-54) and (VIII) kits for performing a beta secretase assay (claims 70-72). Of the 82 total claims, 3 are independent (claims 1, 21 and 73).

At the outset, Applicants observe numerous inconsistencies that demonstrate that the restriction requirement is improper. For example, claim 1 defines a genus containing far more than 52 peptides but is divided into 53 groups of only one peptide each. Thus, the restriction of claim 1 is incomplete (by failing to include its entire scope) and inappropriate, in that the rules contemplate examination of "a reasonable number of species" (37 C.F.R. §1.141) and not a single species. Claim 21 overlaps in subject matter with claim 1, but is divided into seven allegedly separate groups from claim 1, and each of these seven groups, in turn, is overlapping.

Under "traditional" restriction practice, the Applicants might have expected the claims to be divided into peptide compositions, methods of screening claims, methods of treating claims and the like. Thus, the inventions defined by the filed claims should be completely protectable with, at most, an eight divisional applications as delineated above. In almost any other jurisdiction in the world, and under PCT practice, the Applicants would have an expectation that all of the claims would be examined simultaneously under a rational unity of invention standard.

However, in the present case, ***the Examiner has seen fit to issue a 442-way restriction requirement*** for the 82 pending claims. The Examiner arrived at this incredible number by splitting each of the claims into multiple groups. Claim 1 alone has been determined to claim 52 distinct inventions. Such a restriction requirement ignores the unifying characteristic for the claims, namely, that they are all directed to methods and compositions of making and using peptide substrates of human aspartyl protease.

Restriction practice under 35 U.S.C. §121 allows the Commissioner discretion to require restriction between two or more "independent ***and*** distinct" inventions (See M.P.E.P. 802.01 defining independent and distinct). Referring to M.P.E.P. 802.01 to ascertain the meaning of "independent" in relation to this practice, Applicants and Examiner's alike are instructed that the term means

> " means that there is no disclosed relationship between the two or more subjects disclosed, that is, they are ***unconnected in design, operation, or effect***, for example: (1) species under a genus which species are not usable together as disclosed; or (2) process and apparatus incapable of being used in practicing the process."

In the case of the present invention, the claims of the present invention are not "independent" as defined above. Taking for example the peptide/polypeptide subject matter

of claims 1-35 and 73-82, the subject matter of those claims is directly connected in design (*i.e.*, the protein or peptide sequences all comprise a scissile bond that is cleaved by a human aspartyl protease), they operate in the same manner (*i.e.*, the peptides are cleaved by human aspartyl protease), and have the same effect (*i.e.*, mimic the effects of wild-type substrate for human aspartyl protease).

Moreover, the M.P.E.P. instructs Examiners that "if a search and examination of an entire application can be made without serious burden, the examiner ***must examine it on its merits even if it includes claims to independent or distinct inventions***." There are two criteria for proper restriction for restriction between patentably distinct inventions:

> (A) The inventions must be independent or distinct as claimed and
>
> (B) There must be a ***serious burden*** on the examiner if restriction is required.

The Examiner has simply failed to establish that there is a serious burden to examine all of the claims. M.P.E.P. § 803 requires that the Examiner "***must provide reasons and/or examples in support of conclusions***" Hence, the Examiner has the burden of presenting a *prima facie* showing that restriction is necessary. Here, the Examiner has simply listed all of the sequences as separate groups and stated, in conclusory terms, that restriction is required without providing any explanation or reasoning as to why it would be a serious burden to examine all the claims. In the absence of such reasoning, Applicants have no way of providing a rebuttal argument. Essentially the Examiner has abandoned his burden and instead presented in its place a command that Applicants prove to his satisfaction that restriction is not required. Applicants protest, for this is not the Applicants' task, establishing that a restriction is necessary, is a burden that lies firmly with the Examiner, and Applicants request the Examiner either meets this burden or withdraws the requirement.

IV. Conclusion and Request for Reconsideration.

Applicants submit that the Examiner has failed to articulate a proper restriction requirement and that the claimed invention should not be restricted 442 ways. It would not be unduly burdensome for the Examiner to consider all the substrates of the claimed invention as one group. A more appropriate and traditional restriction would be

between Groups I through VIII listed at page 4 above. In light of the above response, Applicants respectfully request that the restriction requirement be reconsidered and withdrawn or modified. Should the Examiner wish to discuss this response in further detail, Applicants invite the Examiner to telephone the undersigned representative.

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Respectfully submitted,

By _____

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APPENDIX A
MARKED VERSION OF AMENDMENTS

[58]64. A method for identifying agents that modulate the activity of Asp2 aspartyl protease, comprising the steps of:

(a) contacting an Asp2 aspartyl protease and a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35 in the presence and absence of a test agent, wherein the Asp2 aspartyl protease is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3;

(b) determining the cleavage of said peptide or fusion protein between said P_1 and said P_1' site by said Asp2 in the presence and absence of the test agent; and

(c) comparing the cleavage activity of said Asp2 in the presence of the test agent to the cleavage activity in the absence of the agent to identify agents that modulate the activity of the polypeptide, wherein a modulator that is an Asp2 inhibitor reduces said cleavage and a modulator that is an Asp2 agonist increases said cleavage.

[67]66. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) growing a cell in the presence and absence of a test agent, wherein the cell expresses an Hu-Asp2 and expresses a protein comprising a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35;

(b) determining the determining the cleavage of said protein at the site between said P_1 and P_1' in said cell in the presence and absence of the test agent; and

(c) comparing said cleavage activity in the presence of the test agent to the cleavage activity in the absence of the test agent to identify an agent that inhibits the activity of Hu-Asp2, wherein reduced cleavage activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

[68]67. A method according to claim [67]66, wherein the host cell has been transformed or transfected with a polynucleotide comprising a nucleotide sequence

that encodes a Hu-Asp2, wherein said nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 2;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 4;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 2) or Hu-Asp2(b) (SEQ ID NO: 4), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.

APPENDIX B
COMPLETE LIST OF PENDING CLAIMS

1. An isolated peptide comprising a sequence of at least four amino acids defined by formula P_2P_1--$P_1'P_2'$ wherein

P_2 is a charged amino acid, a polar amino acid, or an aliphatic amino acid but is not an aromatic amino acid;

P_1 is an aromatic amino acid or an aliphatic amino acid but not a polar amino acid or a charged amino acid;

P_1' is a charged amino acid, or aliphatic amino acid, or a polar amino acid but is not an aromatic amino acid;

P_2' is an uncharged aliphatic polar amino acid or an aromatic amino acid; and

wherein said peptide is cleaved between P_1 and P_1' by a human aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:3 and said peptide does not comprise the corresponding P_2P_1--$P_1'P_2'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

2. The isolated peptide of claim 1, comprising an amino acid sequence defined by formula P_2P_1--$P_1'P_2'P_3'$, wherein P_3' is any amino acid, and wherein said peptide does not comprise the corresponding P_2P_1--$P_1'P_2'P_3'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

3. The isolated peptide of claim 1, comprising an amino acid sequence defined by formula $P_3P_2P_1$--$P_1'P_2'P_3'$, wherein P_3 is an uncharged polar amino acid, an uncharged aliphatic amino acid, or an aromatic amino acid, and wherein said peptide does not comprise the corresponding $P_3P_2P_1$--$P_1'P_2'P_3'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

4. The isolated peptide of claim 3, comprising an amino acid sequence defined by formula $P_4P_3P_2P_1$--$P_1'P_2'P_3'$, wherein said P_4 is a charged amino acid, a polar amino acid or an aliphatic amino acid but not an aromatic amino acid and said peptide does not comprise the corresponding $P_4P_3P_2P_1$--$P_1'P_2'P_3'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

5. The isolated peptide of any one of claims 2 through 4, further comprising an amino acid at position P_4' immediately to the carboxy-terminal position of P_3' wherein said P_4' is any amino acid said, and wherein the peptide does not comprise the corresponding $P_3P_2P_1$--$P_1'P_2'P_3'$ P_4' portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

6. The isolated peptide of claim 1, wherein said P_2 is an amino acid selected from the group consisting of N, L, K, S, G, T, D, A, Q and E.

7. The isolated peptide of claim 1, wherein said P_1 is an amino acid selected from the group consisting of Y, L, M, Nle, F, and H.

8. The isolated peptide of claim 1, wherein said P_1' is an amino acid selected from the group consisting of E, A, D, M, Q, S and G.

9. The isolated peptide of claim 1, wherein said P_2' is an amino acid selected from the group consisting of V, A, N, T, L, F, and S.

10. The isolated peptide of claim 2, wherein said P_3' is an amino acid selected from the group consisting of E, G, F, H, cysteic acid and S.

11. The isolated peptide of claim 3, wherein said P_3 is an amino acid selected from the group consisting of A, V, I, S, H, Y, T and F.

12. The isolated peptide of claim 4, wherein said P_4 is an amino acid selected from the group consisting of E, G, I, D, T, cysteic acid and S.

13. The isolated peptide of any one of claims 4-12, wherein said P_4' is an amino acid selected from the group consisting of F, W, G, A, H, P, G, N, S, and E.

14. The isolated peptide of any one of claims 1 through 13 further comprising a first label.

15. The isolated peptide of claim 14 further comprising a second label.

16. An isolated peptide according to any one of claims 1-13, further comprising a detectable label and a quenching moiety, wherein cleavage of the peptide between P_1 and P_1' separate the quenching moiety from the label to permit detection of the label.

17. The isolated peptide of claim 10 or 12, wherein said cysteic acid further comprises a covalently attached label.

18. The isolated peptide of any one of claims 1-17, wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP β- secretase cleavage sequence: SEVKM-DAEFR (SEQ ID NO:20).

19. The isolated peptide of any one of claims 1-17, wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP Swedish KM NL mutation, β- secretase cleavage sequence SEVNL-DAEFR (SEQ ID NO:19).

20. The isolated peptide of claim 1, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17, SEQ ID NO:18; SEQ ID NO:120; SEQ ID NO:133; SEQ ID NO:134; SEQ ID NO:135; SEQ ID NO:136; SEQ ID NO:137; SEQ ID NO:138; SEQ ID NO:141; SEQ ID NO:143; SEQ ID NO:144; SEQ ID NO:145; SEQ ID NO:147; SEQ ID NO:148; SEQ ID NO:149; SEQ ID NO:150; SEQ ID NO:151; SEQ ID NO:152; SEQ ID NO:153; SEQ ID NO:154; SEQ ID NO:155; SEQ ID NO:156; SEQ ID NO:157; SEQ ID NO:158; SEQ ID NO:159; SEQ ID NO:160; SEQ ID NO:161; SEQ ID NO:162; SEQ ID NO:163; SEQ ID NO:164; SEQ ID NO:165;

SEQ ID NO:166; SEQ ID NO:167; SEQ ID NO:168; SEQ ID NO:169; SEQ ID NO:190; SEQ ID NO:191; SEQ ID NO:192 and SEQ ID NO:193.

21. An isolated peptide comprising a sequence of at least four amino acids defined by formula P_2P_1--$P_1'P_2'$, wherein:

P_2 comprises an amino acid selected from the group consisting of N, S, and D;

P_1 comprises an amino acid selected from the group consisting of Y, L, and Nle;

P_1' comprises an amino acid selected from the group consisting of E, A, and D;

P_2' comprises an amino acid selected from the group consisting of A and V; and

wherein a human Aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3 (Hu-Asp2) cleaves said peptide between P_1 and P_1';

with the proviso that if $P_1'P_2'$ comprise the sequence DA, P_2P_1 do not comprise the sequences NL or NNle.

22. An isolated peptide according to claim 21, wherein the peptide amino acid sequence consists of 4-50 amino acids.

23. An isolated peptide according to claim 21, wherein the Hu-Asp2 cleaves the peptide at a rate greater than the Hu-Asp2 cleaves a corresponding peptide having the P_2P_1--$P_1'P_2'$ amino acid sequence KMDA.

24. An isolated peptide according to claim 21, wherein the Hu-Asp2 cleaves the peptide at a rate greater than the Hu-Asp2 cleaves a corresponding peptide having the P_2P_1--$P_1'P_2'$ amino acid sequence KMDA.

25. A peptide according to claim 21, further comprising a label.

26. A peptide according to claim 21, further comprising a label and a quenching moiety that quenches the label, wherein the label and quenching moiety are attached on opposite sides of the P_1--P_1 peptide bind, whereby cleavage of the P_1--P_1 peptide bond separates the label and quenching moiety.

27. A polypeptide comprising a peptide sequence according to claim 21, and further comprising a transmembrane domain to localize the polypeptide to a cellular membrane when the polypeptide is expressed in a eukaryotic cell.

28. A polypeptide comprising a peptide according to any one of claims 1 through 20 and further comprising a transmembrane domain amino acid sequence.

29. A polypeptide according to claim 28, wherein the peptide is N-terminal to the transmembrane domain.

30. The polypeptide of claim 28 or 29, wherein the peptide and the transmembrane domain are separated by a linker.

31. The polypeptide of claim 30, wherein said linker is a peptide linker comprising between about 20 to about 40 amino acids.

32. The polypeptide according to any one of claims 28-31, wherein said transmembrane domain anchors said polypeptide to an intracellular membrane selected from the group consisting of the Golgi or the endoplasmic reticulum.

33. The fusion protein of any of claims 28-32, wherein said transmembrane domain is selected from the group consisting of the transmembrane domain of galactosyltransferase, the transmembrane domain of sialyly transferase; the transmembrane domain of human aspartyl transferase 1; the transmembrane domain of human aspartyl transferase 2; the transmembrane domain of syntaxin 6; the transmembrane domain of ubiquitin; the transmembrane domain of insulin B chain and the transmembrane domain of APP.

34. The polypeptide according to any one of claims 28-32, further comprising a reporter protein amino acid sequence.

35. The polypeptide of claim 34, wherein said reporter protein is selected from the group consisting of luciferase; alkaline phosphatase; - galactosidase; - glucorinidase; green fluorescent protein; chloramphenical acetyl transferase;

36. A polynucleotide comprising a nucleotide sequence that encodes a polypeptide according to any one of claims 20-35.

37. A polynucleotide comprising a nucleotide sequence that encodes a peptide according to any one of claims 1-27.

38. A vector comprising a polynucleotide according to claim 36.

39. A vector comprising a polynucleotide according to claim 37.

40. A vector according to claim 38 wherein said polynucleotide is operably linked to a promoter to promote expression of the fusion protein encoded by the polynucleotide in a host cell.

41. A host cell transformed or transfected with a polynucleotide according to claim 36.

42. A host cell transformed or transfected with a vector according to any one of claims 38-40.

43. A method for assaying for modulators of - secretase activity, comprising the steps of:

(a) contacting a first composition with a second composition both in the presence and in the absence of a putative modulator compound, wherein the first composition comprises a mammalian - secretase polypeptide or biologically active fragment thereof, and wherein the second composition comprises a substrate, wherein said substrate comprises a peptide according to any of claims 1 through 26 or a polypeptide according to any of claims 27-35;

(b) measuring cleavage of the substrate peptide in the presence and in the absence of the putative modulator compound; and

(c) identifying modulators of - secretase activity from a difference in cleavage in the presence versus in the absence of the putative modulator compound, wherein a modulator that is a - secretase antagonist reduces such cleavage and a modulator that is a - secretase agonist increases such cleavage.

44. The method of claim 43, wherein said first composition comprises a purified human Asp2 polypeptide.

45. The method of claim 43, wherein said first composition comprises a soluble fragment of a human Asp2 polypeptide that retains Asp2 - secretase activity.

46. The method of claim 45, wherein said soluble fragment is a fragment lacking an Asp2 transmembrane domain.

47. A method according to claim 43, wherein the - secretase polypeptide of the first composition comprises a polypeptide purified and isolated from a cell transformed

or transfected with a polynucleotide comprising a nucleotide sequence that encodes the - secretase polypeptide.

48. A method according to claim 43, wherein the polypeptide of the first composition is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide, and wherein the measuring step comprises measuring APP processing activity of the cell.

49. The method claim of any of claims 43-48, further comprising a step of treating Alzheimer 's Disease w ith an agent identified as an inhibitor of Hu-Asp2.

50. A - secretase modulator identified according to the method of any of claims 43-48.

51. A method of inhibiting - secretase activity *in vivo* comprising a step of administering a modulator according to claim 50 that is a - secretase antagonist to a mammal in an amount effective to inhibit - secretase in cells of said mammal.

52. A method of producing a substrate for a - secretase assay comprising:
growing a host cell transformed or transfected with a vector of claim 40 in a manner allowing expression of said polypeptide.

53. The method of claim 52, further comprising purifying said polypeptide.

54. The method of claim 52, wherein said host cell is selected from the group consisting of a mammalian host cell, a bacterial host cell and a yeast host cell.

55. A pharmaceutical composition comprising a modulator of claim 50 and a pharmaceutically acceptable carrier.

56. A method of treating a disease or condition characterized by an abnormal - secretase activity comprising administering to a subject in need of treatment a pharmaceutical composition of claim 55.

57. A use of a modulator identified according to the method claim 43 in the manufacture of a medicament for the treatment of Alzheimer' s Disease.

58. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) contacting a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27-35 and a composition comprising an Hu-Asp2 activity in the presence and absence of a test agent;

(b) determining the cleavage of said peptide or polypeptide between said P_1 and P_1' by said Hu-Asp2 in the presence and absence of the test agent; and

(c) comparing said cleavage activity of the Hu-Asp2 in the presence of the test agent to the activity in the absence of the test agent to identify an agent that inhibits said cleavage by the Hu-Asp2, wherein reduced activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

59. A method according to claim 58, wherein the Hu-Asp2 is a recombinant Hu-Asp2 purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes Hu-Asp2.

60. A method according to claim 58,

wherein the Hu-Asp2 is expressed in a cell, wherein the contacting comprises growing the cell in the presence and absence of the test agent, and wherein the determining step comprises measuring cleavage of said peptide or fusion protein.

61. A method according to claim 60, wherein the cell further comprises a polynucleotide encoding the polypeptide, and wherein the contacting step comprises growing the cell under conditions in which the cell expresses the polypeptide.

62. A method according to claim 60 or 61, wherein the cell is a human embryonic kidney cell line 293 cell.

63. A method according to any one of claims 59-62 wherein the nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 2;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 4;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 2) or Hu-Asp2(b) (SEQ ID NO: 4), wherein said fragment

exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.

64. A method for identifying agents that modulate the activity of Asp2 aspartyl protease, comprising the steps of:

(a) contacting an Asp2 aspartyl protease and a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35 in the presence and absence of a test agent, wherein the Asp2 aspartyl protease is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3;

(b) determining the cleavage of said peptide or fusion protein between said P_1 and said P_1' site by said Asp2 in the presence and absence of the test agent; and

(c) comparing the cleavage activity of said Asp2 in the presence of the test agent to the cleavage activity in the absence of the agent to identify agents that modulate the activity of the polypeptide, wherein a modulator that is an Asp2 inhibitor reduces said cleavage and a modulator that is an Asp2 agonist increases said cleavage.

65. A method according to 58 or 64, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2.

66. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) growing a cell in the presence and absence of a test agent, wherein the cell expresses an Hu-Asp2 and expresses a protein comprising a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35;

(b) determining the determining the cleavage of said protein at the site between said P_1 and P_1' in said cell in the presence and absence of the test agent; and

(c) comparing said cleavage activity in the presence of the test agent to the cleavage activity in the absence of the test agent to identify an

agent that inhibits the activity of Hu-Asp2, wherein reduced cleavage activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

67. A method according to claim 66, wherein the host cell has been transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes a Hu-Asp2, wherein said nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 2;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 4;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 2) or Hu-Asp2(b) (SEQ ID NO: 4), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.

68. A method according to any one of claims 66-67, further comprising a step of treating Alzheimer's Di sease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

69. The use of an agent identified as an inhibitor of Hu-Asp2 according to any one of claims 66-67 in the manufacture of a medicament for the treatment of Alzheimer's Disease.

70. A kit for performing a - secretase assay comprising a - secretase substrate comprising a peptide according to any of claims 1 through 27 and a - secretase enzyme.

71. The kit of claim 70, wherein said - secretase substrate is a polypeptide according to any of claims 28-35.

72. The kit of claim 70 or 71, further comprising reagents for detecting the cleavage of said peptide or fusion protein.

73. An isolated peptide comprising a sequence of at least 10 amino acids having the sequence SEISY-EVEFR (SEQ ID NO:152).

74. The isolated peptide of claim 73, wherein said peptide comprises at least 3 amino acids immediately to the carboxy-terminal of SEISY-EVEFR (SEQ ID NO:152).

75. The isolated peptide of claim 73, wherein said peptide comprises at least 3 amino acids immediately to the amino-terminal of SEISY-EVEFR (SEQ ID NO:152).

76. The isolated peptide of claim 73, wherein said peptide comprises at least 5 amino immediately to the carboxy-terminal of SEISY-EVEFR (SEQ ID NO:152).

77. The isolated peptide of claim 73, wherein said peptide comprises at least 5 amino immediately to the amino-terminal of SEISY-EVEFR (SEQ ID NO:152).

78. The isolated peptide of claim 73, wherein said peptide comprises at least 10 amino immediately to the amino-terminal of SEISY-EVEFR (SEQ ID NO:152).

79. The isolated peptide of claim 73, wherein said peptide comprises at least 13 amino acids.

80. The isolated peptide of claim 73, wherein said peptide comprises at least 15 amino acids.

81. The isolated peptide of claim 73, wherein said peptide comprises at least 20 amino acids.

82. The isolated peptide of claim 73, wherein said peptide comprises at least 50 amino acids.

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The Patent Office is hereby requested to acknowledge receipt of the following papers by stamping and returning this card.

Yan et al.

09/908,943

Petition for one month Extension of Time including Authorization to debit account for fee.
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	Examiner	Art Unit	
	Charles L. Patterson, Jr.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-82* is/are pending in the application.

4a) Of the above claim(s) *1-20 and 28-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election with traverse of Group 56, claims 21-27 wherein P_1 is Y in Paper No. 10 is acknowledged. The traversal is on the ground(s) that there has been no showing that there is a serious burden upon the examiner to examine several of the groups and that the inventions must be independent and distinct. Applicants suggest 8 groups that the invention should be restricted to. This is not found persuasive because it is maintained that it would be a very serious burden upon the examiner to examine all of the groups that applicants suggest combining. The examination of all of groups 1-35 and 73-82 as one group as suggested by applicant would require the search of 52 different specific sequences as well as claims 1 and 21 that are drawn to a multitude of different peptides, claim 1 more so than claim 21. The examiner could have grouped claims 1-19 into many different groups because of all of the possible combinations of different charged, polar, aliphatic of aromatic amino acids in claim 1, but he chose not to in order to simplify the restriction requirement. Each of the peptides of claims 1-35 and 73-82 are structurally different and therefore properly restricted. In addition, claims 1 and 21 are limited to being cleaved by protease molecules of SEQ ID NO:1 or 3 and the examiner could have split these claims and those depending on them into twice as many groups because of this, but he chose not to do so. Claim 1 and dependent claims also are limited to peptides that are not 16 different sequences and the examiner could have split these claims into 16 groups, but he chose not to do so. The examiner also could have had applicant elect one particular SEQ ID NO as their invention and not even taken into account claims 1 and 21 because they involve so many sequences, but he chose not to do this. The search of 52 different sequences would in itself be an unreasonable burden upon the examiner and that doesn't even take into account the search of claims 1 and 21, which read on numerous embodiments.

As to the argument that the groups must be both independent and distinct, in MPEP § 802.01 the meaning of "independent" and "distinct" is discussed, along with a discussion of the legislative history of these terms in patent law. It is concluded in MPEP § 803 that restriction is proper when the inventions "are either independent (MPEP § 806.04 - §806.04(i)) or distinct (MPEP § 806.05 - § 806.05(i))" (emphasis added). The examiner does not agree that in any other jurisdiction and in PCT practice there would be a different restriction requirement or unity of invention requirement.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-20 and 28-82 and claims 21-27 wherein P_1 is not Y are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is apparently incorrect in the recitation of "P_1--P_1 bind" in line 3 and "P_1--P_1 bond" on line 4. Apparently the first recitation should be "bond" instead of "bind". There is no "P_1--P_1 bond" as these are the same residues. Apparently "P_1--P_1' bond" was intended in each instant.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to millions upon millions of embodiments. The claims are limited to any peptide having 4 or more amino acids meeting the requirements of claim 21 as to what P_2, P_1, P_1' and P_2' are. This reads on any protein of any length having the limitations of claim 21. The limits are such that when the STIC did the search there were so many hits that it crashed the hard disk and the whole search system. They had to put another limitation into the search to even be able to search the structure of claim 21 and then even they got an extremely large number of hits. Applicants have not enabled the making and/or using of all of the embodiments of the instant claims. Whether or not a particular peptide sequence will be cleaved by the protein encoded by SEQ ID NO:1 or 3 cannot be ascertained by the office and would require obtaining the peptide and testing it with the two proteases. The office does not have facilities to do such testing and must rely upon applicants to do this.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-27 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over either of Semerjian, et al. (U), Van Camp, et al. (V), Lowell, et al. (W) or Sellar, et al. (X). Semerjian, et al. teach a peptide that contains the sequence DYDA in Fig. 3, the line having "960" at the end, Van Camp, et al. teach a peptide that contains SYDA at positions 132-135 of Fig. 2, Lowell, et al. teach a peptide that contains NYDA a positions 40-43 of Fig. 6 and Sellar, et al. teach a peptide that contains NYDA at positions 40-43 of Fig. 1. The patent office does not have the facilities to test the instant peptides to see if the proteases of the instant claims will cleave these peptides or whether they contain a transmembrane domain, but absent convincing proof to the contrary it is maintained that they do. The addition of a label to aid in the assay would have been obvious. This rejection is being done under 102/103 since it is not known whether the peptides are cleaved by the proteases, but since they meet the requirements of the instant claims as to sequence it is maintained that they are.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 703-308-1834. The examiner can normally be reached on Monday - Friday, 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone number is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
February 14, 2003

Notice of References Cited	Application/Control No. 09/908,943	Applicant(s)/Patent Under Reexamination YAN ET AL.	
	Examiner Charles L. Patterson, Jr.	Art Unit 1652	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Semerjian, A.V, et al. (1989) J. Mol. Biol. 207, 1-13.
	V	Van Camp, W., et al. (1990) Proc. Natl. Acad. Sci., USA 87, 9903-9907.
	W	Lowell, C.A., et al. (1986) J. Biol. Chem. 261(18), 8442-8452.
	X	Sellar, G.C., et al. (1981) J. Biol. Chem. 266(6), 3505-3510.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Form PTO-1449 (Modified)

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U.S. Department of Commerce
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT

(Use several sheets if necessary)

Atty. Docket No.	Serial No.
29915/00281A	09/908,843
Applicant	
Yan *et al.*	
Filing Date	**Group**
July 19, 2001	~~1645~~ 1653

U.S. PATENT DOCUMENTS

*Examiner Initials		Document Number	Issue Date	Name	Class	Subclass	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

*Examiner Initials		Document Number	Publication Date	Country	Class	Subclass	Translation	
							Yes	No
CH	B1	WO 00/17369	~~30/03/2000~~ 3/30/00	WIPO	—	—		

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

CH	C1	Haass *et al.*, "Processing of β -Amyloid Precursor Protein in Microglia and Astrocytes Favors an Internal Localization over Constitutive Secretion", *The Journal of Neuroscience*, **11(12)**:3783-3793
CH	C2	Kang *et al.*, "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor", *Nature*, **325**:733-736 (1987)
CH	C3	Kitaguchi *et al.*, "Novel precursor of Alzheimer's disease amyloid protein shows protease inhibitory activity", *Nature*, **331**:530-532 (1988)
CH	C4	Lin *et al.*, "Inhibition of Cathepsin D by Synthetic Oligonucleotides", *The Journal of Biological Chemistry*, **254**:11875-11883 (1979)
CH	C5	Lin *et al.*, "Human aspartic protease memapsin 2 cleaves the β -secretase site of β-amyloid precursor protein", *PNAS*, **97**:1456-1460 (2000)
CH	C6	Ponte *et al.*, "A new A4 amyloid mRNA contains a domain homologous to serine proteinase inhibitors", *Nature*, **331**:525-527 (1988)

EXAMINER	DATE CONSIDERED
C Belitzer	2/13/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 (Modified)

U.S. Department of Commerce
Patent and Trademark Office

DEC 10 2001 PATENT & TRADEMARK OFFICE JC556

INFORMATION DISCLOSURE STATEMENT

(Use several sheets if necessary)

Atty. Docket No.	Serial No.
29915/00281A	09/908,843
Applicant: Yan *et al.*	
Filing Date: July 19, 2001	Group: ~~1645~~ 1653

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)		
	C7	Schechter *et al.*, "On the Active Site of Proteases, III. Mapping the Active Site of Papain; Specific Peptide Inhibitors of Papain", *Biochemical and Biophysical Research Communications*, **32**:898-902 (1968)
	C8	Schechter *et al.*, "On the Size of the Active Site in Proteases, I. Papain", *Biochemical and Biophysical Research Communications*, **27**:157-162 (1967)
	C9	Sinha *et al.*, "Cellular mechanisms of β -amyloid production and secretion", *Proc. Nat'l. Acad. Sci. (USA)*, **96**:11049-11053 (1999)
	C10	Tanzi *et al.*, "Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease", *Nature*, **331**:528-530 (1988)
	C11	Vassar *et al.*, "β -Secretase Cleavage of Alzheimer's Amyloid Precursor Protein by the Transmembrane Aspartic Protease BACE", *Science*, **286**:735-741 (1999(
	C12	Yan *et al.*, "Membrane-anchored aspartyl protease with Alzheimer's disease β -secretase activity", *Nature*, **402**:533-537 (1999)
	C13	Younkin, "Processing of the Alzheimer's Disease β A4 Amyloid Protein Precursor (APP)", *Brain Pathology*, **1**:253-262 (1991)

EXAMINER	DATE CONSIDERED
	2/13/03

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